

U.S.S.N. 09/484,484  
KÖSTER *et al.*  
RESPONSE

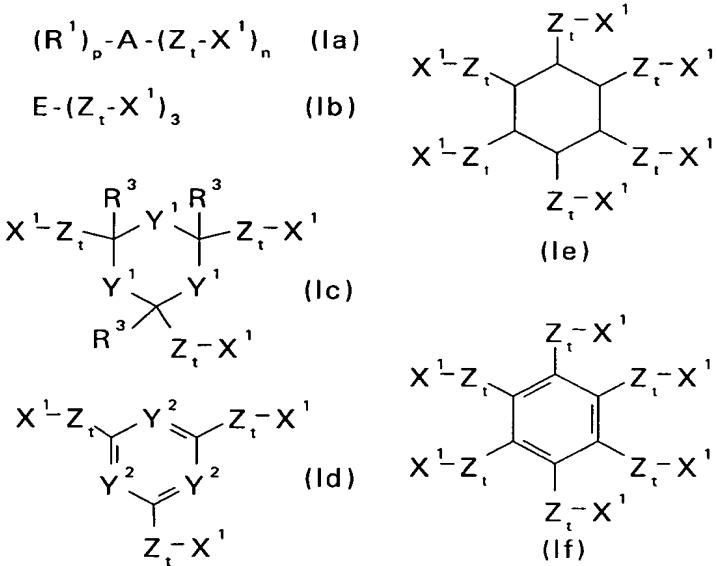
invention. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

**Claims 10, 11, 14-17, 20 and 21**

Claims 10, 11, 14-17, 20 and 21 are rejected as allegedly being indefinite for lacking antecedent basis for recitation of compounds of formulae (IIa), (IIb), (IIc) or (IId). Applicant respectfully disagrees.

As described in detail below, claim 10, and dependent claims 11 and 14-16, are directed to compounds of formulae (Ia) and (Ib) of claim 6 where A is carbon and E is nitrogen. Claim 17, and dependent claims 20 and 21, are directed to compounds of formulae (Ic) and (Id) of claim 6 where Y<sup>1</sup> is CH<sub>2</sub> and Y<sup>2</sup> is CH. Therefore, these claims are properly dependent on claim 6.

Claims 10, 11, 14-17, 20 and 21 are ultimately dependent on claim 6, which is directed to a liquid phase carrier (LPC) of formulae (I):



where:

A is carbon or silicon;

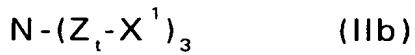
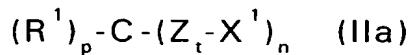
E is nitrogen or P(O);

Y<sup>1</sup> is CH<sub>2</sub>, NH, S or O;

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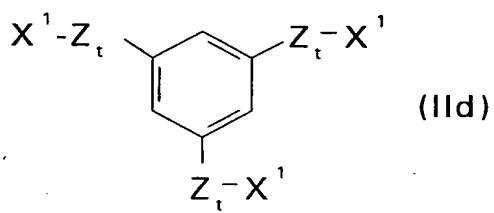
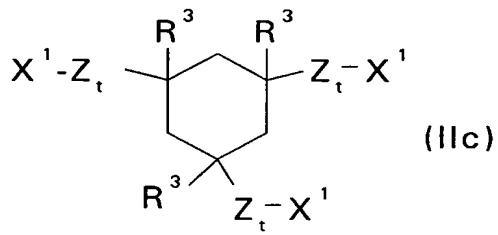
$Y^2$  is selected from CH and N; and  
the remaining variables are as defined therein.

Claim 10, and dependent claims 11 and 14-16, are directed to LPCs of formulae (Ia) and (Ib) where A is carbon and E is nitrogen. Substituting carbon for A in formula (Ia) and nitrogen for E in formula (Ib) results in formulae (IIa) and (IIb) of claim 10:



Therefore, claim 10, and dependent claims 11 and 14-16, are properly dependent on claim 6, and are not indefinite for recitation of formulae (IIa) and (IIb).

Claim 17, and dependent claims 20 and 21, are directed to LPCs of formulae (Ic) and (Id) where  $Y^1$  is  $CH_2$  and  $Y^2$  is CH. Substituting  $CH_2$  for  $Y^1$  in formula (Ic) and CH for  $Y^2$  in formula (Id) results in formulae (IIc) and (IId) of claim 17:



Therefore, claim 17, and dependent claims 20 and 21, are properly dependent on claim 6, and are not indefinite for recitation of formulae (IIc) and (IId).

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**Claims 29 and 49**

Claims 29 and 49 are rejected as allegedly being indefinite because there allegedly is no support for the claimed LPC coupled to a photocleavable moiety or a biopolymer. Applicant respectfully disagrees.

Claim 29 is directed to the LPC of claim 6 that is coupled to a photocleavable linker. LPCs of the instant application coupled to photocleavable linkers are disclosed in the instant specification, for example, at page 36, lines 1-7. Therefore, the instant specification provides support for the claimed subject matter.

Claim 49 is directed to the LPC of claim 6 that is coupled to a biopolymer. LPCs of the instant application coupled to biopolymers are disclosed in the instant specification, for example, at page 2, line 24. Therefore, the instant specification provides support for the claimed subject matter.

Reconsideration and withdrawal of this rejection is respectfully requested.

**REJECTION OF CLAIMS 6, 7, 9, 22, 25, 26, 31, 32, 45 AND 49 UNDER 35 U.S.C. §103(a)**

Claims 6, 7, 9, 22, 25, 26, 31, 32, 45 and 49 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the teachings of U.S. Patent No. 5,198,540, to Köster *et al.* It is alleged that the species of LPCs disclosed in the cited reference render the instantly claimed LPCs *prima facie* obvious. Applicant respectfully traverses this rejection.

**Relevant Law**

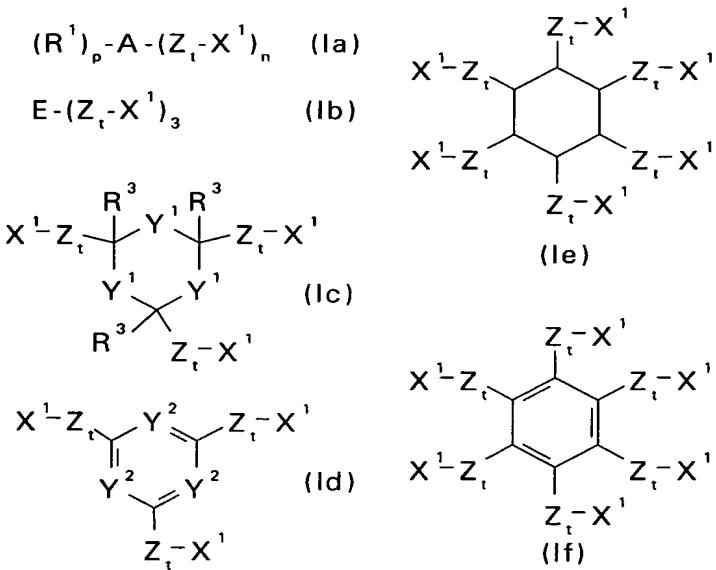
[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

#### The instant claims

Instant claim 6 is directed to a liquid phase carrier (LPC) of formulae (I):



where:

A is carbon or silicon;

E is nitrogen or P(O);

Y<sup>1</sup> is CH<sub>2</sub>, NH, S or O;

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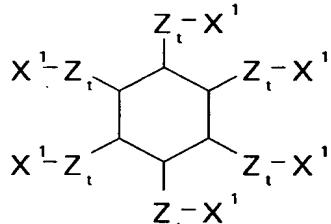
Y<sup>2</sup> is selected from CH and N;

n is 3 or 4; and

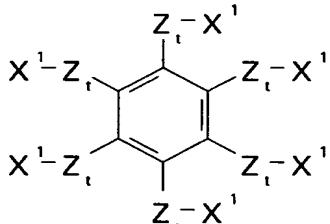
the remaining variables are as defined therein.

Claims 7 and 9 further define the variables in claim 6.

Claim 22 is directed to an LPC of claim 6 that has formulae (Ie) or (If):



(Ie)



(If)

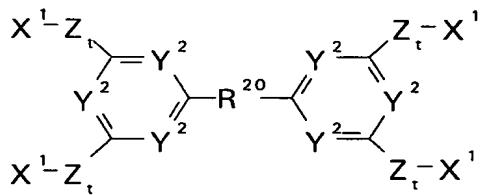
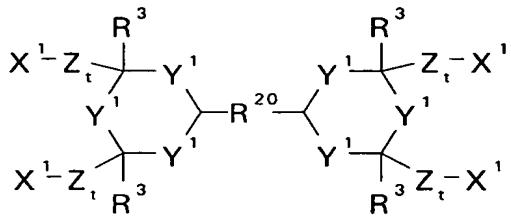
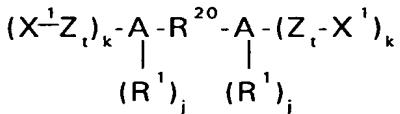
where the variables are as defined therein. Claims 25 and 26 further define the variables in claim 22.

Claims 31 and 32 are directed to specific LPCs not disclosed in the cited reference.

Claim 39 is directed to a method of solution phase biopolymer synthesis using an LPC of formulae (I). Claim 40 specifies certain LPCs for use in the method of claim 39. Claim 47 specifies certain monomers for use in the method of claim 39.

Claim 45 is directed to an LPC of formulae:

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where the variables are as defined therein.

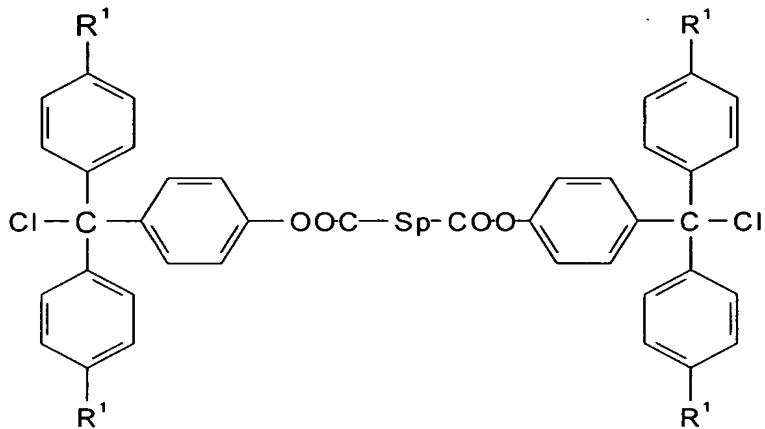
Claim 48 is directed to a method of solution phase biopolymer synthesis using an LPC of formulae (I) where the protocol used in the synthesis of the biopolymer is the phosphoramidite protocol.

Claim 49 is directed to the LPC of claim 6 coupled to a biopolymer.

**Differences between the teachings of Köster et al. and the instant claims**

U.S. Patent No. 5,198,540, to Köster et al., teaches LPCs possessing two to four points of attachment of formula  $Sp(X)_n$ , where X is a reactive group which is compatible from the point of view of nucleotide chemistry, n is an integer from 2 to 4, and Sp is an optionally branched alkylene or polyalkylene group, an arylene or polyarylene group, a polyaralkylene group, a polyester, a polyamide, a polysiloxane, an optionally branched alkyleneoxy compound or optionally partially alkylated polyalkyleneoxy compound. The cited reference also teaches LPCs possessing two points of attachment having formulae:

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$$\text{X}-\text{OC}-\text{Sp}-\text{CO-X}$$

The cited reference does not teach or suggest LPCs of formulae (I) possessing 3 to 6 points of attachment, as required by instant claims 6, 7 and 9. Nor does the cited reference teach or suggest LPCs of formulae (Ie) or (If) possessing 6 points of attachment, as required by instant claims 22, 25 and 26. The reference also does not teach or suggest the specific LPCs claimed in instant claims 31 and 32. Nor does the reference teach or suggest the LPCs of instant claim 45 that possess 4, 5 or 6 points of attachment.

Furthermore, the cited reference does not teach or suggest methods of using LPCs possessing 3 to 6 points of attachment in solution phase biopolymer synthesis, as claimed in instant claims 39 and 48. Nor does the cited reference teach or suggest methods of solution phase biopolymer synthesis using the specific LPCs of claim 40.

Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. The cited reference does not teach or suggest the structural modifications required to modify the LPCs taught therein to arrive at the instantly claimed LPCs. It is respectfully submitted that one of ordinary skill in the art, given the teachings of U.S. Patent

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No. 5,198,540, would not have been motivated to prepare the LPCs of the instant claims for use in solution phase biopolymer synthesis. Absent such motivation, the instant claims are not *prima facie* obvious over the teachings of the cited reference.

**Therefore, the Office Action fails to establish a *prima facie* case of obviousness**

In order to establish a *prima facie* case of obviousness, there must be some teaching or suggestion in the cited art that would motivate one of ordinary skill in the art to do what applicant has done. It is respectfully submitted that no such motivation exists in U.S. Patent No. 5,198,540. The cited reference teaches a generic class of LPCs possessing 2 to 4 points of attachment. The cited reference does not teach or suggest the instantly claimed classes of LPCs of formulae (I) possessing 3 to 6 points of attachment. Nor does the cited reference teach or suggest LPCs of formulae (Ie) or (If) possessing 6 points of attachment, as required by instant claims 22, 25 and 26. The reference also does not teach or suggest the specific LPCs claimed in instant claims 31 and 32. Nor does the reference teach or suggest the LPCs of instant claim 45 that possess 4, 5 or 6 points of attachment.

Since the cited reference does not teach or suggest the LPCs of the instant claims, it cannot teach or suggest methods of solution phase biopolymer synthesis using the LPCs of the instant claims, nor can it teach or suggest the LPCs of the instant claims coupled to a biopolymer. Therefore, the Office Action has failed to set forth a *prima facie* case of obviousness.

**Notwithstanding the failure to establish a *prima facie* case of obviousness, the LPCs of the instant claims possess properties not taught or suggested by the cited reference**

Furthermore, as taught in the instant specification and as described in the attached unexecuted DECLARATION of KÖSTER, the LPCs of the instant claims possess properties not taught or suggested by U.S. Patent No. 5,198,540. As described in the specification (see, *e.g.*, page 7, lines 25-27), use of the LPCs

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of the instant application and claims in solution phase biopolymer synthesis provides biopolymers of higher yield and purity than those taught in the cited reference.

Specifically, as described in Example 7 of the instant specification, use of a trivalent LPC of the instant claims, dT<sub>3</sub>-Aryl-LPC, in solution phase oligonucleotide synthesis provides the desired 10-mer in an overall yield of 33%. The cited reference teaches, in Table 1, use of the divalent LPCs taught therein in oligonucleotide synthesis to afford the a 5-mer, 6-mer and a 7-mer in overall yields of 14%, 8% and 5%.

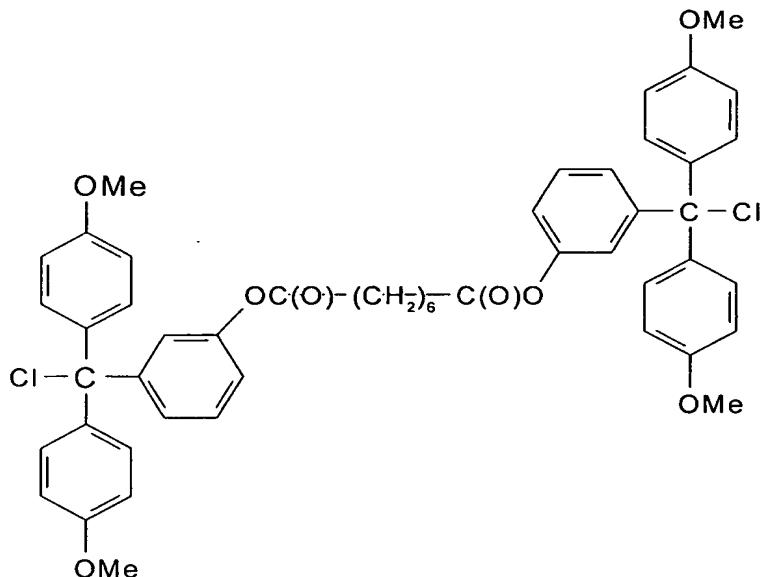
The increase in yield obtained using the multivalent LPCs (*i.e.*, those possessing 3 to 6 points of attachment) of the instant application is neither taught nor suggested by the cited reference, which teaches use of divalent LPCs. The cited reference would not have provided one of ordinary skill in the art motivation to have prepared and tested the LPCs of the instant claims. Nor does the cited reference teach or suggest the structural modifications required to achieve the above-noted increase in solution phase biopolymer synthesis yield. Therefore, the instant claims are not obvious over the teachings of U.S. Patent No. 5,198,540.

**The Declaration of Köster**

Provided herewith is an unexecuted DECLARATION of KÖSTER demonstrating the increase in solution phase biopolymer synthesis yield achieved with the LPCs of the instant claims versus the results provided in U.S. Patent No. 5,198,540 for solution phase biopolymer synthesis using the divalent LPCs taught therein. As shown in EXAMPLE 7 of the instant specification and in the DECLARATION, use of an LPC of the instant claims possessing 3 points of attachment (1,3,5-tris[9-(2'-deoxythymidin-3'-O-yl)-2,5-diaza-1,6,9-trioxononyl]-benzene (dT<sub>3</sub>-Aryl-LPC)) in solution phase oligonucleotide synthesis provides an increased yield of the desired product as

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compared to solution phase oligonucleotide synthesis using the following LPC of the cited reference, which possesses two points of attachment:



Specifically, use of the LPC of the instant claims provides a 10-mer oligonucleotide in an overall yield of 33%, as compared to overall yields of a 5-mer, 6-mer and a 7-mer of 14%, 8% and 5% using the LPC of the cited reference. The structural modifications required to achieve this increase in yield are not taught or suggested by the cited reference. Therefore, the instant claims are not obvious over the teachings of U.S. Patent No. 5,198,540.

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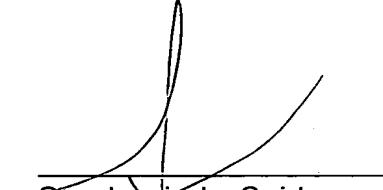
Applicant respectfully requests reconsideration and withdrawal of this rejection.

\* \* \*

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,  
**HELLER EHRMAN WHITE & McAULIFFE LLP**

By:

  
Stephanie L. Seidman  
Registration No. 33,779

Attorney Docket No. 24743-2301B

**Address all correspondence to:**

Stephanie L. Seidman, Esq.  
HELLER EHRMAN WHITE & McAULIFFE LLP  
4350 La Jolla Village Drive, 7th Floor  
San Diego, California 92122  
Telephone: (858) 450-8400  
Facsimile: (858) 587-5360  
EMAIL: [sseidman@hewm.com](mailto:sseidman@hewm.com)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: KÖSTER *et al.*  
Serial No.: 09/484,484  
Confirmation No.: 9747  
Filed: January 18, 2000  
For: *SOLUTION PHASE BIOPOLYMER  
SYNTHESIS*  
Art Unit: 1623  
Examiner: Wilson, J.

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**ATTACHMENTS TO RESPONSE TO OFFICE ACTION**

The following attachments are provided:

(1) An unexecuted DECLARATION of KÖSTER.